

combined function of all components of the hypothalamo-pituitary-adrenal axis, adrenocortical function is still often assessed solely by the increment in plasma corticosteroid concentration produced by exogenous corticotrophin (Sampson *et al.*, 1962; Wood *et al.*, 1965; Ansari *et al.*, 1969). We have emphasized that assessment of the response to stress is essential (Malone *et al.*, 1970), and in the studies reported here it is clear that without this assessment incorrect conclusions regarding the integrity of the hypothalamo-pituitary-adrenal axis might have been reached. In 13 out of 14 asthmatic children daily corticotrophin treatment does not seem to have produced suppression of pituitary function in terms of ability to respond to hypoglycaemic stress.

The average time taken for a normal response to hypoglycaemia to develop in these patients was 14.7 months (range 3-24 months). This time is rather longer than that found in adult subjects by Livanou *et al.* (1967). They found that after withdrawal of steroids, and without using corticotrophin therapy, only one patient (with an adrenocortical adenoma) had an abnormal response to hypoglycaemia more than 12 months after withdrawal of steroid therapy. One patient in the present study, who took two months to show a plasma corticosteroids response to corticotrophin, still had an abnormal corticosteroid response to hypoglycaemia 36 months after conversion to corticotrophin.

Assessment of time spent in hospital was possible only in six patients who had sufficient hospital admissions before and after

the change in treatment regimen. From the results obtained (Table IV) the control of asthmatic symptoms was more satisfactory on corticotrophin, but the group studied was small and there may have been an element of bias, since after starting corticotrophin all the patients were seen regularly by only one physician. This could have resulted in a diminished admission rate, although it is less likely that the duration of stay in hospital would have been altered appreciably.

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Vitamin D Intoxication Treated with Porcine Calcitonin

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Summary

Porcine calcitonin was used to treat three patients with hypercalcaemia due to vitamin D intoxication. In two patients a rapid and sustained fall to normal in serum calcium occurred within three days, in the third patient normocalcaemia was achieved in seven days. In view of its rapid and sustained effect calcitonin may be of value in the urgent treatment of hypercalcaemia due to vitamin D intoxication.

Introduction

Poisoning with vitamin D is now less frequent than formerly when vitamin D was prescribed for a variety of skin and arthritic disorders. Yet cases still occur and the associated hypercalcaemia may be life-threatening. The patient becomes anorexic, nauseated, develops mental impairment, and may lapse into coma, while cardiac arrhythmias and renal failure may occur. In severe cases urgent treatment of the hypercalcaemia is required.

The calcium-lowering hormone, calcitonin, has been shown to be active in man (Milhaud, Bourichin, Moukhtar, and Perault-Staub, 1965; Foster, Joplin, MacIntyre, Melvin, and Slack, 1966), and we report here the treatment with porcine

calcitonin of three hypercalcaemic patients with vitamin D intoxication.

Case 1

A 69-year-old woman with hypoparathyroidism was admitted to hospital in a drowsy and confused state. She had been unwell for three weeks, complaining of anorexia, constipation, and increased thirst. She had previously had a subtotal thyroidectomy and was first seen one year previously with hypocalcaemia. Her initial investigations showed a serum calcium of 3.8 mg/100 ml, phosphate 8.8 mg/100, and an alkaline phosphatase of 7-9 K.A. units. The plasma proteins were 8.0 g/100 ml (albumin 3.7 g, globulin 4.3 g) and the blood urea was 40 mg/100 ml. While hypocalcaemic her plasma did not contain any detectable immunoassayable parathyroid hormone (Buckle, 1968). A diagnosis of hypoparathyroidism was made and she was treated with oral calcium and calciferol 1.25 mg (50,000 units) a day. The plasma calcium rose and stabilized at concentrations of 8.9-9.6 mg/100 ml and the dosage of calciferol was reduced to 1.25 mg (50,000 units) twice a week. It was later ascertained that for four weeks before admission she had mistakenly taken calciferol 7.5 mg (300,000 units) a day.

On examination she was lethargic and mentally confused. There was muscular hypotonia and the tendon reflexes were depressed. Her urine contained protein. The initial serum calcium was 15.1 mg/100 ml, and a repeat eight hours later was 15.8 mg/100 ml, plasma phosphate 5.3 mg/100 ml, and the alkaline phosphatase 8 K.A. units. The plasma proteins were 7.3 g/100 ml (albumin 3.6 g, globulin 3.7 g). The blood urea was 196 mg/100 ml.

Progress—Porcine calcitonin 40 M.R.C. units was given intravenously twice daily by injection over five minutes and, in addition, a continuous intravenous infusion of porcine calcitonin 120 M.R.C. units in 500 ml of normal saline was administered every 12 hours (Fig. 1). One hour after the first injection of calcitonin

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the serum calcium fell from 15.8 to 15.0 mg/100 ml, after 12 hours of infusion it had fallen to 14.0 mg/100 ml, and after a further 12 hours to 13.0 mg/100 ml. The serum calcium fell to normal by 60 hours. Calcitonin was stopped after three and a half days, and thereafter the serum calcium remained normal apart from a transient rise to 10.9 mg/100 ml on one occasion.

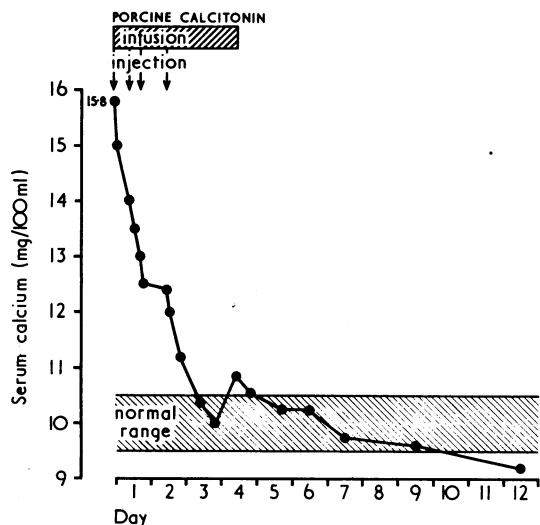


FIG. 1—Case 1. Effect of porcine calcitonin on serum calcium concentration.

Case 2

A 64-year-old woman, previously diagnosed as suffering from hypoparathyroidism and receiving treatment with calcium and calciferol, was admitted as an emergency after being found unconscious in the street. She had had a subtotal thyroidectomy 43 years previously, and had been seen two years previously complaining of cramps in the limbs. Her initial investigations showed a serum calcium of 6.3 mg/100 ml, and a phosphate of 5.6 mg/100 ml. The plasma proteins were 7.0 g/100 ml (albumin 4.1 g, globulin 2.9 g) and blood urea was 31 mg/100 ml. She was treated with calcium supplements by mouth and intermittent courses of calciferol. For the three months before admission she had received calciferol 2.5 mg (100,000 units) orally on alternate days. She complained of six weeks' increasing constipation and cramp-like abdominal pains, and lost consciousness on four occasions.

On examination she was drowsy and mentally slow. There was generalized weakness in the limbs, but the tendon reflexes were normal. Investigations showed serum calcium 13.2 mg/100 ml and phosphate 4.7 mg/100 ml. The blood urea was 93 mg/100 ml.

Progress.—The patient was treated with porcine calcitonin 40 M.R.C. units intravenously twice daily, together with a slow infusion of porcine calcitonin 120 M.R.C. units every 12 hours. The serum calcium fell by 1.6 mg/100 ml within 12 hours and had fallen to 9.6 mg/100 ml by 48 hours (Fig. 2). Thereafter the

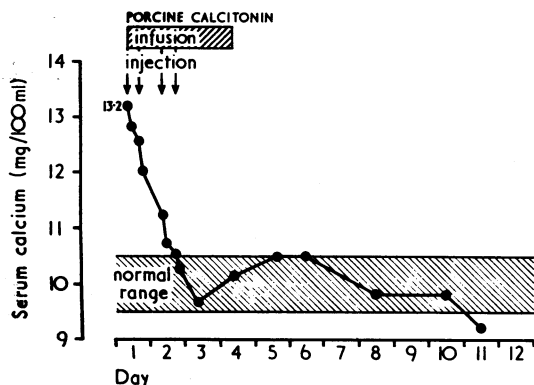


FIG. 2—Case 2. Effect of porcine calcitonin on serum calcium concentration.

serum calcium remained normal apart from a temporary rise to 10.6 mg/100 ml. Calcitonin treatment was stopped on the fourth day.

Case 3

A 62-year-old asthmatic woman was admitted with weakness of the arms and legs and mental confusion. She had been asthmatic for 40 years and had been treated with steroids for the last three years. Nine months before admission she had complained of backache and had been treated with increasing doses of oral calciferol. During the last two months she had received calciferol 10 mg (400,000 units) a day by mouth and 600,000 units once a week by injection.

On examination she was disorientated and hallucinated. There was weakness of the arms and legs, and the ankle reflexes were absent. Investigations showed a serum calcium of 13.1 mg/100 ml, phosphate 3.8 mg/100 ml, and an alkaline phosphatase of 9 K.A. units. The plasma proteins were 6.8 g/100 ml (albumin 3.5 g, globulin 3.3 g). The blood urea was 68 mg/100 ml.

Progress.—Treatment with steroids was continued. During the first few days she deteriorated further and became more confused and drowsy. The serum calcium rose to 14.3 mg/100 ml and the blood urea to 126 mg/100 ml. Treatment was started with porcine calcitonin 40 M.R.C. units by intravenous injection twice a day, together with a slow intravenous infusion of porcine calcitonin 120 M.R.C. units every 12 hours. Transient falls in serum calcium of 1.0-1.5 mg/100 ml followed the acute injections of calcitonin (Fig. 3) and the mean serum calcium fell to 12 mg/100 ml by the

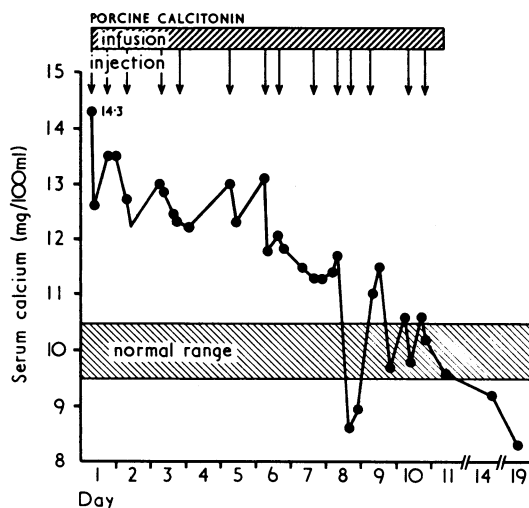


FIG. 3—Case 3. Effect of porcine calcitonin on serum calcium concentration.

sixth day. After the eighth day of treatment it fell to normal and remained so apart from two short-lived episodes of mild hypercalcaemia. Calcitonin was stopped on the fourteenth day.

Discussion

Calcitonin caused the serum calcium to fall to normal in all three patients. Rapid falls of 1.0-1.5 mg/ml occurred during the first one to three hours. In cases 1 and 2 the serum calcium reached normal by the second and third day respectively. In Case 3 serum calcium fell more slowly: acute falls of 1.0-1.5 mg followed individual injections of calcitonin, but some rise in serum calcium occurred between injections. Hypercalcaemia did not recur in any patient after treatment was stopped.

Steroid therapy is often effective in hypercalcaemia due to vitamin D overdosage (Dent, Flynn, and Nabarro, 1953; Anderson, Harper, Dent, and Philpot, 1954; Verner, Engel, and McPherson, 1958) and normocalcaemia may be achieved after five to seven days, although in severe cases the fall in calcium may be delayed for two to three weeks (Anderson

et al., 1954; Verner *et al.*, 1958). The faster action of calcitonin may, therefore, be of greater value than steroids in the treatment of severe cases, when urgent therapy is required. It is of interest that our third patient developed hypercalcaemia while she was already receiving steroid therapy.

Other methods of treatment of hypercalcaemia are available, but none are ideal (Lancet, 1967). Sodium edetate is only temporary in its effect and is nephrotoxic (Foreman, Finnegan, and Leabaugh, 1956). Sodium phosphate is effective (Dent, 1962; Goldsmith and Ingbar, 1966) but may produce metastatic calcification, and its use is potentially hazardous in vitamin D intoxication in which renal calcification may have occurred already.

Vitamin D increases the gastrointestinal absorption of calcium (Jones and Rapoport, 1931; Henneman, Dempsey, Carroll, and Albright, 1956) and this is partly responsible for the hypercalcaemia in vitamin D intoxication. Serum calcium falls slowly if such patients are placed on a low dietary calcium intake (Howard and Meyer, 1948) and part at least of the hypocalcaemic effect of steroids is due to their action in decreasing calcium absorption (Dent *et al.*, 1953; Anderson *et al.*, 1954).

Excess vitamin D increases the rate of resorption of bone. Animals poisoned with vitamin D have a lessened mineral content in their bones and are in negative calcium balance (Hess, Weinstock, Rivkin, 1929; Hess, Benjamin, and Gross, 1931; McLean, 1941). If vitamin D acted solely to increase the gastrointestinal absorption of calcium then a positive calcium balance would be expected. The increased rate of bone resorption may therefore be the major factor responsible for the hypercalcaemia in vitamin D overdosage.

The hypocalcaemic effect of calcitonin is small in normal subjects (Foster *et al.*, 1966; Bijvoet, Sluys Veer, and Jansen, 1968). Its main action is to directly inhibit bone resorption (Raisz, Au, Friedman, and Niemann, 1968; Reynolds, Dingle, Gudmundsson, and MacIntyre, 1968) and it is disputed whether it influences bone deposition. It has no effect on calcium absorption but does have a small calciuric effect (Cochran, Peacock, Sachs, and Nordin, 1970). Calcitonin is most effective in conditions of increased bone resorption, as in Paget's disease and thyrotoxicosis (Bijvoet *et al.*, 1968). The marked hypocalcaemic effect found in all three patients suggests that the increased rate of bone resorption is the major factor responsible for hypercalcaemia in vitamin D intoxication.

Vitamin D has a long biological half-life and hypercalcaemia due to vitamin D overdosage may continue for six to nine months (Howard and Meyer, 1948). The action of calcitonin is rapid in onset and the half-life of circulating porcine calcitonin in man is less than 10 minutes (Buckle, 1971). It was of interest therefore that the hypocalcaemic effects of calcitonin were sustained after treatment was stopped. The reason for this is not clear, although Pak, Wills, Smith, and Bartter (1968) reported a

similar sustained hypocalcaemic effect in a patient with a parathyroid carcinoma.

No patient developed any significant hypocalcaemia and toxic side effects were not encountered. Treatment of hypercalcaemia due to vitamin D intoxication with calcitonin seems to be an effective and safe procedure.

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